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Research Report

What goads cigarette smokers to smoke? Neural adaptation and the mirror neuron system

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ABSTRACT

One model of addiction suggests that neural circuits in the frontal cortex adapt to drug use and become sensitized leading to excessive attribution of incentive salience to drug-associated cues. The present study examined changes associated with cigarette use in the frontal mirror neuron system (MNS) of the human brain, as reflected in mu rhythm responsiveness. Mirror neurons in premotor cortex exhibit visuomotor properties that allow them to respond to self-movement as well as the observation of movement. This is a potential neural substrate for imitation learning and social cognition, factors that may be important in determining who does and does not develop addictive behaviors. EEG mu rhythm suppression is hypothesized to reflect MNS activity and thus provide a non-invasive method for studying this relationship. Our results show that while nonsmokers exhibit normal mu suppression to observed and self-generated actions, smokers exhibit normal suppression only to self-movement but not to the observation of movement, particularly actions involving addiction-related cues. Non-abstinent and abstinent smokers (those abstaining for approximately 12 h) did not differ significantly in their responses to the observation of movement, i.e., both exhibited atypical patterns of mu rhythm reactivity compared to nonsmokers. These data support the hypothesis that cigarette use produces short- and longer term adaptations in the MNS. Such adaptations may inappropriately bias attention toward motivationally salient, addiction-related cues leading to more impulsive and addiction-related behaviors.

1. Introduction

Although the underlying neural mechanisms of addiction have yet to be fully elucidated there is substantial evidence to suggest that genetic, biological, cognitive and social factors play critical roles (Koob and LeMoal, 2001; Robinson and Berridge, 2000). Many cognitive theories of drug addiction, such as aberrant learning theories, are based on the development of conditioned associations through repeated drug exposure. These associations have been implicated in the acquisition, maintenance, and relapse of compulsive drug-taking behavior (Siegel and Ramos, 2002). Beyond pleasure and pain as mediating factors, most aberrant learning hypotheses argue that drugs produce abnormally strong or aberrant

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associations involved in reward learning, associations that are more powerful than natural reward associations. Implicit models of aberrant learning (Tiffany, 1999) explain addiction as over-learned habits that become so automatic that they essentially become compulsive (a habit-learning stimulus–response or S–R model).[1] The formation of S–R habits, however, cannot account for the compulsive and yet flexible nature of drug-seeking behavior. It has been suggested that this requires an additional motivational explanation.

Robinson and Berridge (2000) and Robinson and Kolb (2004) have suggested that addictive drugs alter brain systems involved in motivated behavior. More specifically, drugs affect systems such as the ventral striatum, amygdala, and nucleus accumbens that are responsible for mediating the attribution of incentive salience. It is proposed that these neural circuits adapt and become hypersensitive to drugs, to their physiological effects, and to drug-associated cues. Furthermore, it is speculated that this adaptation occurs primarily through up-regulation of the mesolimbic DA system. Such 'neural sensitization' leads to excessive attribution of incentive salience to drug-related representations, inducing a psychological or compulsive "wanting" of the drug. Furthermore, systems mediating incentive salience can be dissociated from those that mediate the hedonic or pleasurable effects of drugs—or "liking" system.

The widespread release of DA has been suggested to result in a series of adaptations in neural circuits well beyond saliency and reward and that involve motivation, drive, memory, conditioning, control and disinhibition (Robinson and Kolb, 2004; Volkow, 2004). These neural adaptations can lead to enhanced and long-lasting dysregulation of areas such as the orbitofrontal cortex (salience attribution), prefrontal cortex (judgment and inhibitory control), and cingulate cortex (inhibitory control, attention and impulsivity) among others (Volkow, 2004). It is theorized that compulsive drug taking behavior emerges from the increase in motivational drive for the drug, strengthened by conditioned responses, coupled with a decrease in judgment and inhibitory control. It is in this sense that we hypothesize that the compensatory nature of the brain's response to drugs also leads to the neural sensitization of the frontal MNS in the human brain.

Although mirror neurons cannot be studied directly in humans, the existence of homologous cells in or near Brodmann's area 44 has been supported by indirect population-level measures such as TMS (Fadiga et al., 1999) and fMRI (Iacoboni et al., 1999). In addition to its responsiveness to low-level, motor-related imagery, the human MNS has been implicated in higher level cognition. Rizzolatti and Craighero (2004) and Umilta et al. (2001), for example, have suggested that the capacity to associate the visual representation of an observed action with the motor representation of that action can lead to imitative learning. Oberman and colleagues recently reported evidence for a dysfunctional mirror system in high functioning individuals diagnosed with autism spectrum disorders (ASD) (Oberman et al., 2005). ASD are largely characterized by deficits in imitation, pragmatic language, theory of mind, and empathy. Other researchers have suggested that an observation/execution mechanism may underlie the hypothesized evolution of language from an earlier gestural communication system (Rizzolatti and Arbib, 1998). Still others have suggested that once another individual's actions are represented and understood in terms of one's own actions, it is possible to make predictions about the mental state of the observed individual, leading to "theory of mind" capabilities (Gallese, 2003). Lastly, Leslie et al. (2004) found that empathy may critically depend on one's ability to understand the observed facial expression in terms of one's own motor representations. In summary, all these high-level properties suggest that the MNS is part of a broader system that mediates how we relate to others in the world. Because of its critical involvement in social cognition, we suggest that a hypersensitive MNS might enhance responsiveness to immediate social cues leading to more impulsive and addiction-related behaviors.

In a review of the literature, Jentsch and Taylor (1999) argued that chronic exposure to specific drugs (including marijuana, cocaine, and amphetamine) can depress neural processing in frontal regions and distort functions of the prefrontal cortex. Specifically, regions of the frontal cortex involved in inhibitory response control are directly affected by long-term exposure to drugs of abuse. For example, dysfunction in frontostriatal systems involved in cognitive inhibitory control over behavior can lead to behavior unduly dominated by "pre-potent tendencies" resulting in "a condition associated with profound impulsivity that may contribute to compulsive drug-seeking and drug-taking behavior." These effects on frontal corticocortical and frontal corticosubcortical systems are supported by clinical reports that show neuropsychological deficits in addicts are similar to those of patients suffering from prefrontal dysfunction (Bechara and Van Der, 2005).

One drug that appears to produce neural adaptation is nicotine. Nicotine is a psychostimulant that is present in tobacco and thought to be the principal agent involved in tobacco addiction. It acts as an agonist to activate and desensitize nicotinic acetylcholine receptors (nAChRs). Repeated administration of nicotine can produce behavioral and motivational sensitization (Samaha et al., 2005; Miller et al., 2001). The evidence suggests that this is due to the chronic exposure to the drug, which then leads to changes in the density of nAChRs in both humans and animals in several brain areas, including frontal cortex (Pidoplichko et al., 2004; Samaha et al., 2005). A major component of nicotine's addictive power is its direct effects on the mesolimbic dopaminergic system. Pidoplichko et al. (2004) have identified three main actions that regulate the activity of midbrain dopamine (DA) neurons. First, nicotine activates and then desensitizes nAChRs on DA neurons. This directly excites the neurons for a short period of time before the nAChRs desensitize. Second, nicotine enhances glutamatergic excitation. Finally, nicotine decreases GABAergic inhibition. All these events increase the probability for synaptic plasticity, including long-term potentiation, with the consequence being a relatively long-lasting heightened activity of midbrain DA neurons.

[1] FFT (fast Fourier transform); fMRI (functional magnetic resonance imaging); MNS (mirror neuron system); nAChR (nicotinic acetylcholine receptor); S–R (stimulus–response).